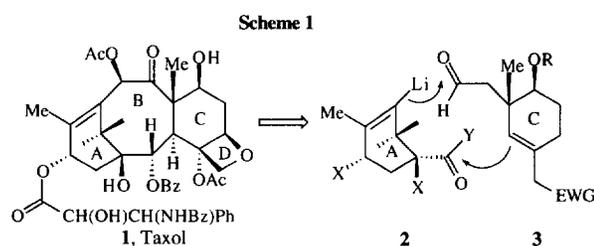


Concise Synthesis of Taxol A-Ring Components: Remote Diastereoselective Additions of Alkenyl Lithiums to Aldehydes

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Abstract: The acid chloride **6** provides access to **7** (R,S and S,S) which upon bromine-lithium exchange undergoes remarkably highly diastereoselective additions to aldehydes; **7** is also readily elaborated into the acetal **10**.
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One of the most direct and convergent approaches to the synthesis of the highly functionalized taxol core structure¹ is depicted in **Scheme 1**.² Construction of the A-ring component and the C-ring unit allows for a multitude of ways to subsequently link them together, one of which is the union of **2** and

3.³ To explore this, and other options, we required a short route to the A-ring **2** (or equivalent) in an enantiomerically enriched form. While there have been many reports describing the synthesis of the taxol A-ring in various oxidation levels,⁴ the chemistry described here uncovered some new observations which are useful for the specific case of taxol, but also should be valuable in the broader arena of synthesis.

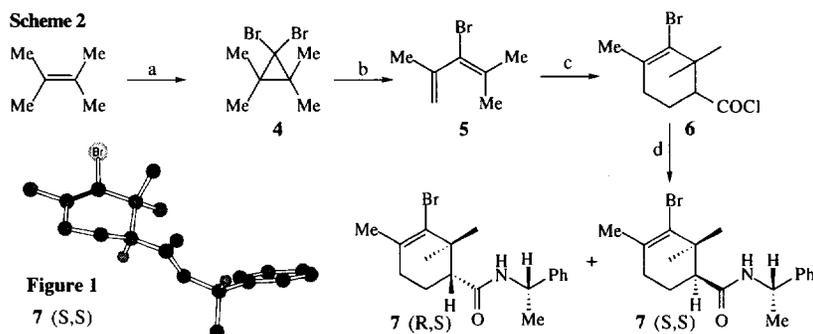


Figure 1
7 (S,S)

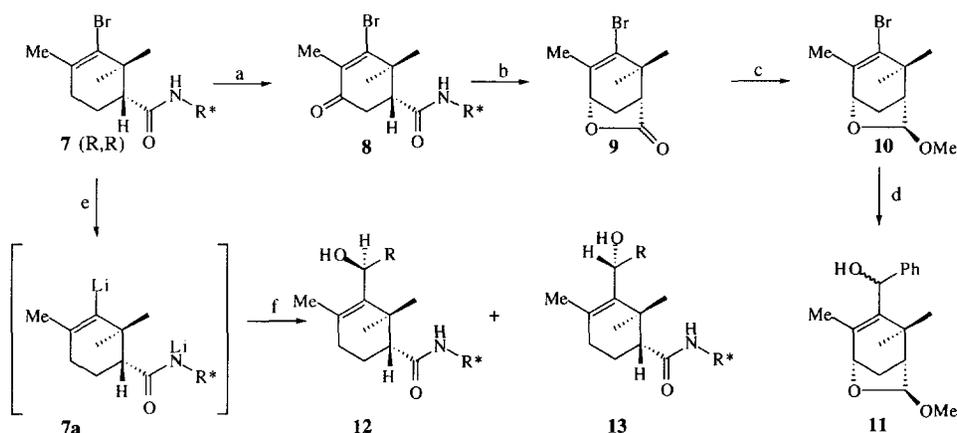
Conditions: -a) $\text{CHBr}_3/t\text{-BuOK/pentane}$, **4** (95%). b) $\text{PhNMe}_2/148^\circ\text{C}$, **5** (>95%). c) $\text{CH}_2\text{CHCOCl}/110^\circ\text{C}$, **6** (95%). d) $S\text{-(-)-PhCHMeNH}_2$, **7** (100%).

Tetramethylethylene was converted into the *gem*-dibromocyclopropane **4**, which on treatment with PhNMe_2 at 148°C gave the bromodiene **5**, **Scheme 2**.⁵ This modification of the literature procedure more than doubles the yield of **5** and is amenable to large scale (100 g). The diene **5** reacted cleanly with acryloyl chloride in a thermal (110°C) Diels-Alder process to give **6** (95%), with no more than traces of the other regioisomer

(<5%). All attempts to catalyze this reaction with chiral Lewis acids, or chiral derivatives of acryloyl chloride were unsuccessful.⁶ Consequently, **6** was treated with *S*-(-)-PhCHMeNH₂ to give a 1:1 mixture of **7** (R,S) and **7** (S,S) which were readily separable, and the absolute stereochemistry of one of the diastereomers determined by X-ray crystallography. **Figure 1** show a Chem 3D representation from the x-ray coordinates of the **7** (S,S) diastereomer, and therefore the other diastereomer **7** (R,S) corresponds to the correct absolute configuration needed for the synthesis of taxol.

Since the *sec*-amide formation to give **7** had accomplished the resolution of the A-ring we decided to examine halogen-metal exchange on this derivative rather than the traditional esters, **Scheme 3**.

Scheme 3 [R* = R-(+) PhCHMe or S-(-) PhCHMe]



Conditions: -a) CrO₃/3,5-DMP/CH₂Cl₂/-15°C **8** (76%). b) i. N₂O₄/CCl₄/CHCl₃/-40 to 0°C (96%). ii. 0.1 M NaOH/80°C (66%). iii. MeI/acetone/K₂CO₃ (89%). iv. NaBH₄/MeOH/-15°C (91%). v. K₂CO₃/PhCl/135°C **9** (76%). c) DIBAL-H/CH₂Cl₂/-78°C, followed by (MeO)₃CH/MeOH/CSA **10** (68%). d) *t*-BuLi/Et₂O/-78°C, followed by PhCHO **11** (80%, 3:2). e) *t*-BuLi (6 eq.)/Et₂O/-78°C/3 h. f) RCHO (10 eq.)/-78°C/Et₂O, **12/13**.

Treatment of **7** (**TABLE 1**) with *t*-BuLi (6 equiv. in hexane) gave the dianion **7a** which was quenched with an aldehyde to give two diastereomers **12** and **13** (R = Me, Et, Ph and *t*-BuCH₂). Remarkably, even though the newly created stereogenic center is 7 atoms removed from the chiral benzylic position and 4 atoms from C-1, the observed diastereoselectivity is extraordinarily high. In the case of acetaldehyde (R = Me) the ratio was 20:1, and the structure of the major product was determined by X-ray crystallography, **Figure 2**.

TABLE 1

| Substrate | Solvent | Base | Aldehyde | Prods | Yield % | By-prodt |
|----------------|-------------------|----------------------|---------------------------------|--------|---------|----------|
| 7 (R,R) | Et ₂ O | <i>t</i> -BuLi (hex) | MeCHO | 20 : 1 | 60 | Alkene |
| 7 (R,R) | THF | <i>t</i> -BuLi (hex) | MeCHO | 20 : 1 | 30 | Alkene |
| 7 (R,R) | Et ₂ O | <i>t</i> -BuLi (hex) | EtCHO | 15 : 1 | 65 | Alkene |
| 7 (R,R) | Et ₂ O | <i>t</i> -BuLi (hex) | PhCHO | 7 : 1 | 50 | Alkene |
| 7 (S,R) | Et ₂ O | <i>t</i> -BuLi (hex) | PhCHO | 6 : 1 | 80 | Alkene |
| 7 (R,R) | Et ₂ O | <i>t</i> -BuLi (hex) | <i>t</i> -BuCH ₂ CHO | 10 : 1 | 50 | Alkene |
| 7 (S,R) | Et ₂ O | <i>t</i> -BuLi (hex) | <i>t</i> -BuCH ₂ CHO | 10 : 1 | 50 | Alkene |

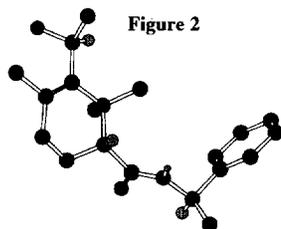
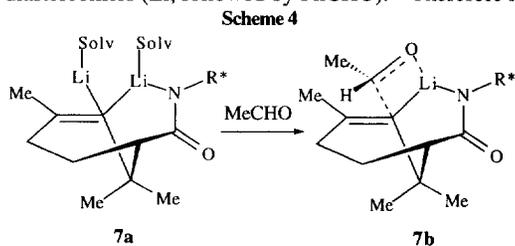


Figure 2

The only significant by-products were the alkene **7** (Br replaced by H), and small amounts of compounds that were derived from *o*-metallation of the phenyl ring followed by quenching with the aldehyde. Also, in order to establish that **12** and **13** are diastereomers only at *sec*-OH position and no epimerization at C-1 has taken place, we subjected the mixture of **12** and **13** to the Dess-Martin oxidation conditions to give a single enone.

By way of attempted comparison, the C-1 derivatives -CONMeR*, -CO₂Bu' and -CO-oxazolidinone of **6** did not undergo clean halogen metal exchange, and from the complex mixtures obtained the only discernible product(s) were attack of the *t*-BuLi on the C-1 carbonyl group. The *sec*-amide in **7** thus provides a protecting facility for C-1 through the amide anion **7a**.

While it is possible to introduce the C-13 oxygen functionality into very advanced taxol intermediates⁷ we were intrigued with the possibility of subjecting **7** to allylic oxidation reactions. A priori, an electron-deficient vinyl bromide might be rather resistant towards this type of transformation, and indeed perusal of the literature did not reveal any pertinent examples other than the oxidation of a vinyl iodide to a β-iodoenone during the course of Kishi's approach to taxol.⁸ In the event, treatment of **7** with CrO₃·3,5-dimethylpyrazole⁹ gave the required β-bromo enone **8** (76%).¹⁰ *N*-Nitrosation of **8**, followed by hydrolysis, esterification, reduction and lactonization gave the known lactone **9**.¹¹ The lactone was reduced with DIBAL-H and the crude lactol treated with CH(OMe)₃/MeOH/H⁺ to give **10**. Bromine-lithium exchange (*t*-BuLi) of **10** and quenching with PhCHO gave **11** (80%) as a 3:2 mixture of diastereomers. Wender has reported that the lactone **9** gave a 3.1:1 ratio of diastereomers (Li, followed by PhCHO).¹⁰ Therefore it appears that the *sec*-amide is the source of the enhanced



diastereoselectivity, presumably through a possible lithium-bridged chelate.¹² It is probable that the dilithio species **7a** is in fact a bridged compound, and the more sophisticated representation in **Scheme 4**, as either a solvated monomer or aggregated species, is a more plausible picture. Reaction of **7a** with acetaldehyde would favor **7b**, which leads to the major diastereomer

12. It would seem unlikely that the cause of the diastereoselectivity is confined only to substrate **7**, and we are exploring the notion of long-range lithium chelation (supramolecular) as a more general phenomena to control stereochemistry.¹³

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References and Footnotes.

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